1. SPORADIC CJD (from January 2017)

1.1 **DEFINITE:**

Progressive neurological syndrome **AND**

Neuropathologically **or** immunocytochemically

or biochemically confirmed

1.2 **PROBABLE:**

1.2.1 I + 2 of II and III

OR

1.2.2 I + 2 of II and IV

OR

1.2.3 I + 2 of II and positive 14-3-3

OR

1.2.4 Progressive neurological syndrome and positive RT-QuIC in CSF or other tissues

1.3 **POSSIBLE:**

I + 2 of II + duration < 2 years

I	Rapidly progressive cognitive impairment
II	A Myoclonus
	B Visual or cerebellar problems
	C Pyramidal or extrapyramidal features
	D Akinetic mutism
III	Typical EEG (generalised periodic complexes)
IV	High signal in caudate/putamen on MRI brain scan or at least two cortical regions (temporal, parietal, occipital) either on DWI or FLAIR

2. ACCIDENTALLY TRANSMITTED TSE

2.1 **DEFINITE**

Definite CJD with a recognised iatrogenic risk factor (see box)

2.2 **PROBABLE**

2.2.1 Progressive predominant cerebellar syndrome in human pituitary hormone recipients

2.2.2 Probable CJD with recognised iatrogenic risk factor (see box)

2.3 **POSSIBLE**

Possible CJD with a recognised risk factor
(agreed and EURO meeting Bled, 2006)

RELEVANT EXPOSURE RISKS FOR THE CLASSIFICATION AS IATROGENIC CJD

The relevance of any exposure to disease causation must take into account the timing of the exposure in relation to disease onset

- Treatment with human pituitary growth hormone, human pituitary gonadotrophin or human dura mater graft.
- Corneal graft in which the corneal donor has been classified as definite or probable human prion disease.
- Exposure to neurosurgical instruments previously used in a case of definite or probable human prion disease.

This list is provisional as previously unrecognised mechanisms of human prion disease may occur

3. GENETIC TSE

3.1 DEFINITE

3.1.1 Definite TSE + definite or probable TSE in 1st degree relative

3.1.2 Definite TSE with a pathogenic PRNP mutation (see box)

3.2 PROBABLE

3.2.1 Progressive neuropsychiatric disorder + definite or probable TSE in 1st degree relative

3.2.2 Progressive neuropsychiatric disorder + pathogenic PRNP mutation (see box)

- **PRNP MUTATIONS ASSOCIATED WITH GSS NEUROPATHOLOGICAL PHENOTYPE**

  P102L, P105L, A117V, G131V, F198S, D202N, Q212P, Q217R, M232T, 192 bpi
- **PRNP MUTATIONS ASSOCIATED WITH CJD NEUROPATHOLOGICAL PHENOTYPE**

  D178N-129V, V180I, V180I+M232R, T183A, T188A, E196K, E200K, V203I, R208H, V210I, E211Q, M232R, 96 bpi, 120 bpi, 144 bpi, 168 bpi, 48 bp*del*
- **PRNP MUTATIONS ASSOCIATED WITH FFI NEUROPATHOLOGICAL PHENOTYPE** D178N-129M
- **PRNP MUTATION ASSOCIATED WITH VASCULAR PRP AMYLOID**

  Y145s
- **PRNP MUTATIONS ASSOCIATED WITH PROVEN BUT UNCLASSIFIED PRION DISEASE**

  H187R, 216 bpi,
- **MUTATIONS ASSOCIATED WITH NEURO-PSYCHIATRIC DISORDER BUT NOT PROVEN PRION DISEASE**

  I138M, G142S, Q160S, T188K, M232R, 24 bpi, 48 bpi, 48 bpi + nucleotide substitution in other octapeptides

(additional list of mutations appended)

4. vCJD

4.1 DEFINITE

1A **and** neuropathological confirmation of vCJD[e].

4.2 PROBABLE

4.2.1 I **and** 4/5 of II **and** IIIA **and** IIIB

4.2.2 I **and** IV A[d]

4.3 POSSIBLE

I **and** 4/5 of II **and** III A

I A Progressive neuropsychiatric disorder
B Duration of illness > 6 months
C Routine invesitgations do not suggest an alternative diagnosis
D No history of potential iatrogenic exposure
E No evidence of a familial form of TSE

II A Early psychiatric symptoms[a]
B Persistent painful sensory symptoms[b]
C Ataxia
D Myoclonus or chorea or dystonia
E Dementia

III A EEG does not show the typical appearance of sporadic CJD[c] in the early stages of illness
B Bilateral pulvinar high signal on MRI scan

IV A Positive tonsil biopsy[d]

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a depression, anxiety, apathy, withdrawal, delusions.

b this includes both frank pain and/or dysaesthesia.

c the typical appearance of the EEG in sporadic CJD consists of generalised triphasic periodic complexes at approximately one per second. These may occasionally be seen in the late stages of variant CJD.

d tonsil biopsy is **not** recommended routinely, nor in cases with EEG appearances typical of sporadic CJD, but may be useful in suspect cases in which the clinical features are compatible with vCJD and MRI does not show bilateral pulvinar high signal.

e spongiform change and extensive PrP deposition with florid plaques throughout the cerebrum and cerebellum.

ADDITIONAL LIST OF MUTATIONS

- **PRNP MUTATIONS WITHOUT CLINICAL AND NEUROPATHOLOGICAL DATA**
  T188R, P238S

- **PRNP POLYMORPHISMS WITH ESTABLISHED INFLUENCE ON PHENOTYPE**
  M129V

- **PRNP POLYMORPHISMS WITH SUGGESTED INFLUENCE ON PHENOTYPE**
  N171S, E219K, 24 bp deletion

- **PRNP POLYMORPHISMS WITHOUT ESTABLISHED INFLUENCE ON PHENOTYPE**
  P68P, A117A, G124G, V161V, N173N, H177H, T188T, D202D, Q212Q, R228R, S230S